NOVARTIS

Clinical Development

RFB002/Ranibizumab/Lucentis®

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A 12-months, randomized, VA-assessor blinded, multicenter, controlled phase IV trial to investigate noninferiority of two treatment algorithms (discretion of the investigator vs. pro re nata) of 0.5 mg ranibizumab in patients with visual impairment due to diabetic macula edema

Statistical Analysis Plan (SAP) Addendum

Author: [redacted]

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List of abbreviations

AE	Adverse Event
AIC	Akaike Information Criteria
ANCOVA	Analyses of Covariance
BCVA	Best Corrected Visual Acuity
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
CF	Color Fundus
CFP	Color Fundus Photography
CI	Confidence Interval
CM	Concomitant Medication
CRC	Central Reading Center
cSLO	Confocal Scanning Laser Ophthalmoscope
CSR	Clinical Study Report
CSRT	Central Subfield Retinal Thickness
CSRV	Central Subfield Retinal Volume
DBL	Database Lock
DHP	Data Handling Plan
DI	Discretion of the Investigator
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DRP	Data Review Plan
DRS	Diabetic Retinopathy Scale
DTS	Data Transfer Specification
eCRF	electronic Case Report/Record Form
ELM	External Limiting Membrane
EoS	End of Study
EoT	End of Treatment
ETDRS	Early Treatment of Diabetic Retinopathy Study
[redacted]	[redacted]
FAS	Full Analysis Set
FCP	Foveal Center Point
FPFV	First patient first visit
HbA1c	Glycosylated Hemoglobin
IOP	Intraocular Pressure
IRC	Intraretinal Fluid of Cystoid
IRF	Intraretinal Fluid
[redacted]	[redacted]
IVT	Intravitreal
KM	Kaplan-Meier
LOCF	Last Observation Carried Forward
LPLV	Last patient last visit
LS	Least Square

MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed Model Repeated Measurement
NPDR	Non-Proliferative Diabetic Retinopathy
NEI	National Eye Institute
OCT	Optical Coherence Tomography
PD	Protocol Deviation
PDR	Proliferative Diabetic Retinopathy
PED	Pigment Epithelium Detachment
PLS	Product Lifecycle Services
PK	Pharmacokinetics
PRN	Pro re nata
PRP	Panretinal Photocoagulation
PPS	Per Protocol Set
PT	Preferred Term
RMP	Risk Management Plan
RPE	Retinal Pigment Epithelium
RS	Randomized Set
SAE	Serious AE
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain OCT
SF	Subretinal fluid
SI	Standard International
SOC	System Organ Class
TEAE	Treatment Emergent AE
TFI	Treatment Free Interval
TFLs	Tables, Figures, Listings
VA	Visual Acuity
[redacted]	[redacted]
VI	Visual Impairment
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analysis according to Section 9 of the study protocol (version no. 1 including Amendment 1) along with any additional analyses, specifications or deviations from this protocol planned before unmasking of the data. Determination of sample size is specified in Section 3.

This document is written in the future tense. It will be reviewed and updated (including conversion to past tense) for entry into the clinical study report (CSR) after the analysis has taken place.

1.1 Study design

This is a 12-months, phase IV, randomized, parallel-group, visual acuity (VA) assessor-masked, multi-center, interventional study to assess the efficacy and safety of Discretion of the investigator (DI) vs. Pro re nata (PRN) (as needed) regimens of 0.5 mg ranibizumab intravitreal (IVT) injections for adult patients with Type I or Type II diabetes mellitus and visual impairment (VI) due to diabetic macular edema (DME).

A total of 300 patients from approximately 45 centers across Germany were initially planned to be randomized and assigned into one of the treatment arms in a ratio of 1:1. After new and relevant scientific evidence regarding treatment patterns with ranibizumab was published, recruitment to the study was revised and reduced to a total of 135 patients randomized and assigned in a 1:1 ratio to the treatment arms:

- Arm 1 (discretion of the investigator, DI): Investigational, RFB002, 10 mg/ml
- Arm 2 (pro re nata, PRN): Standard of Care, RFB002, 10 mg/ml

The study duration will be up to 13 months (the period of one month is considered to be equal 30 days):

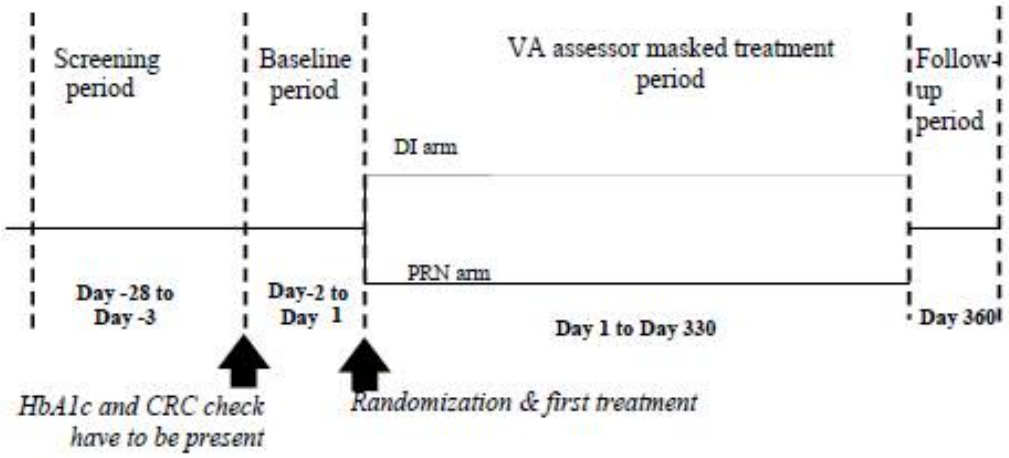
- Screening period: to occur between day -28 and day -3
- Baseline period: to occur between day -2 and day 1
- Treatment period: from baseline (visit 2) to month 11
- Follow-up period: from month 11 to month 12

For patients randomized to the PRN treatment arm the treatment period is from baseline (date of first administration of study treatment) to month 11 with follow-up period up to month 12, whereas for patients randomized to the DI treatment arm the treatment period end date depends on the patient's individual schedule which may occur at the month 11 visit, but not later.

For patients with last injection at the month 11 visit, the follow-up period ends at the month 12 visit; for patients with last injection on or before the month 10.5 visit, the follow-up period ends on or before the month 11.5 visit.

No interim analyses will be performed.

Figure 1-1 Study design



In this study, the VA assessor, who is assessing parameters constituting the primary endpoint (best corrected visual acuity [BCVA]), will be masked to the treatment regimen and will not be allowed to perform any additional study tasks which would unmask him/ her to study treatment. [redacted]

Any personnel involved with the statistical analysis and interpretation of the data and results will be masked until Database Lock (DBL).

Following protocol amendment 1, patient recruitment was revised and reduced. Therefore the original assumed patient number for primary outcome (mean average BCVA change from baseline to month 12) will not be reached; hence all data analysis of this study will be purely exploratory.

1.2 Study objectives and endpoints

The primary objective of this trial is to demonstrate that the mean average change from baseline of BCVA in Early Treatment of Diabetic Retinopathy Study (ETDRS) letters averaged over all post-baseline visits to month 12 in patients with DME treated with ranibizumab injections at the DI and in accordance with disease activity criteria is non-inferior to current standard of care (PRN).

The secondary objectives seek to evaluate:

- Mean change of BCVA in ETDRS letters from baseline to month 12
- Frequency of visits, injections and treatment free intervals (TFIs)
- Mean change of central subfield retinal thickness (CSRT) and foveal center point (FCP) thickness from baseline to month 12
- Change in Diabetic Retinopathy Scale (DRS) from baseline to month 12
- Influence of relevant glycosylated hemoglobin (HbA1c), blood pressure, and blood lipid levels changes on the primary objective

[redacted]:

2 Statistical methods

2.1 Data analysis general information

The analysis will be performed by Novartis Product Lifecycle Services (PLS). SAS® Version 9.4 or higher will be used for generating tables, figures, and listings (TFLs).

Data will be summarized for all patients with respect to background, demographic and baseline characteristics, efficacy and safety observations and measurements.

Descriptive statistics (the number of non-missing observations [n], mean, median, standard deviation [SD], lower quartile [Q1], upper quartile [Q3], minimum, and maximum values) will be presented for continuous variables. The following number of decimal places will be used: mean, median, Q1, and Q3 values to 1 more decimal place than the raw data; minimum and maximum to the same number of decimal places as the raw data and SD to 2 more decimal places than the raw data.

For categorical variables, the number and percentage of each category within a variable will be calculated. If a count of zero is obtained for categorical data, only the zero count (no percentage) will be displayed. If no treatment arm satisfies a category, then the category will be displayed, with the exception of the protocol deviations (PDs) summary. A row (category) denoted "Missing" will be included in count tabulations if a non-zero count of missing values is present for any of the treatment arms. In addition, the corresponding percentage for this row will be displayed.

The study eye is the eye selected by the investigator at baseline (according to the protocol) to receive the study treatment. The fellow eye is the non-study eye.

For non-ocular, study eye, fellow eye and both eyes summary TFLs will be based on all patients included in the analysis population under consideration.

Assessments documented in the database as occurring in "both eyes" will be summarized and listed for both eyes in addition to each eye separately. To facilitate derivations and analysis based on study eye and fellow eye database records for "both eyes" will be split to two records containing identical information as the original record with the exception of the site which shall be recoded to "Right" and "Left", respectively.

The type of retinal disease and the optical coherence tomography (OCT) device used to analyse retinal thickness assessments can lead to variation in results (Han IC and Jaffe GJ 2009, Mylonas et al 2009). Therefore an adjustment to the affected variables will be made, details are provided in Section 2.1.1. The adjusted affected variables will be used for all TFLs, unless stated otherwise.

As the original assumed patient number for the primary outcome will not be reached, the data analysis will be purely exploratory. Nevertheless, statistical testing will still be performed, as stated in the protocol.

All data will be listed by patient, unless stated otherwise.

2.1.1 General definitions

The investigational treatment is 0.5 mg ranibizumab 10 mg/ml solution for injection, taken by patients in two different regimes: PRN or DI.

In this study, PRN is defined as the regime where after initial monthly therapy until maximum BCVA and no signs or no further improvement of disease activity, patients are monitored every month and retreated if any signs of disease activity occur.

DI is defined as the regime where the investigator treats patients at own discretion after initial monthly treatment until maximum BCVA and no signs or no further change of disease activity.

The study treatment period will be defined as starting from baseline (visit 2), which is the date of first administration of study treatment, until the last treatment (laser photocoagulation and/ or ranibizumab) prior to the patient's month 12 (follow-up) visit, which is called the date of last administration of study treatment.

There are two separate treatment phases within the study period:

- an initial treatment phase

  This is the period from first administration of study treatment in the study eye until the first NO treatment given based on the Ranibizumab dose administration electronic Case Report/Record Form (eCRF) when the reason for NO treatment given is one of the following three stability criteria:
  - No disease activity (BCVA maximum, CRT minimum and no further signs of activity in morphologic parameters)
  - Disease activity stable with maximum BCVA (no further improvement of other morphologic parameters)
  - BCVA and disease activity stable (no further improvement of BCVA and other morphologic parameters).

  Note: If the reason for NO treatment given was either:
  - Adverse event
  - Disease activity present but patient refused additional treatment

  the patient will continue to remain in the initial treatment phase until the reason for NO treatment given is one of the aforementioned three stability criteria.
- a maintenance phase

  This is the period from after the end of the initial treatment phase (first NO treatment given based on the Ranibizumab dose administration eCRF) until End of Study (EoS) visit.

The study day for a baseline or post-baseline scheduled or unscheduled visit is defined as

- Study day = (Date of visit) - (Date of baseline visit) + 1

Baseline is the date of first administration of study treatment in the study eye. If a patient is randomized but not treated then the baseline is defined as the date of randomization. Baseline value will be considered as the value of the last assessment collected prior to start of treatment (i.e. data from screening or baseline).

The final contact with patients will be during the 30 days either:

- following the last study visit, or
- following the last administration of study treatment (laser photocoagulation and/ or ranibizumab) if there are post-treatment follow-up visits (whichever is later), including a final contact at the 30-day point.

A re-treatment during the maintenance phase is defined as an administration of study treatment (active ranibizumab) (YES treatment given) following at least one NO treatment given based on the Ranibizumab dose administration eCRF when the reason for NO treatment given is one of the three stability criteria. A patient may have multiple re-treatments.

A TFI is the interval between the first NO treatment given when the reason for NO treatment given is one of the three stability criteria and the first subsequent YES treatment given after that. This will be based on the Ranibizumab dose administration eCRF. A patient may have multiple TFIs.

Note: If a patient had no treatment at month 2, missed month 3 and received treatment at month 4 then we can assume that the duration of each month is 30 days; hence this interval would be 30 + 1 days.

Stability was to be judged by the investigators during the trial. However, to assess compliance with objective stability criteria, the following definitions are introduced:

a) BCVA will not be regarded as stable if there is a change in BCVA of >= 5 letters compared to the previous visit.

b) Retinal thickness (disease activity) will not be regarded as stable if there is a change of >=10% in uncorrected CSRT compared to the previous visit.

Stability compliance assessment will be based on the presence of fluid, BCVA stability, and retinal thickness stability. This will be derived during the maintenance phase when NO treatment given is recorded on the Ranibizumab dose administration eCRF when the reason for NO treatment given is one of the following three stability criteria:

- No disease activity (BCVA maximum, CRT minimum and no further signs of activity in morphologic parameters)
- Disease activity stable with maximum BCVA (no further improvement of other morphologic parameters)
- BCVA and disease activity stable (no further improvement of BCVA and other morphologic parameters).

It will be categorized as follows:

1. No presence of fluid and BCVA stable and retinal thickness stable
2. No presence of fluid and BCVA stable and retinal thickness not stable
3. No presence of fluid and BCVA not stable and retinal thickness stable
4. No presence of fluid and BCVA not stable and retinal thickness not stable
5. Presence of fluid and BCVA stable and retinal thickness stable
6. Presence of fluid and BCVA stable and retinal thickness not stable
7. Presence of fluid and BCVA not stable and retinal thickness stable
8. Presence of fluid and BCVA not stable and retinal thickness not stable

Patients treated not in line with the stability compliance assessment will be deemed as those who according to the definition of the study compliance assessment did not meet the stability criteria but still had a NO treatment given record on the Ranibizumab dose administration eCRF when the reason for NO treatment given is one of the three stability criteria at the same visit. Otherwise they will be regarded as treated in line with the stability compliance assessment.

The stability compliance assessment will be further categorized as:

- Full stability (Yes, No)
  - Yes refers to “No presence of fluid and BCVA stable and retinal thickness stable” (criterion 1 mentioned above)
  - No refers to any of the other categories (criteria 2 to 8 mentioned above)
- Overall full stability (Yes, No)
  - Yes refers to when for each occurrence of NO treatment given due to one of the aforementioned three stability criteria for a patient the stability compliance assessment is always “No presence of fluid and BCVA stable and retinal thickness stable” (criterion 1 mentioned above)
  - No refers to when for each occurrence of NO treatment given due to one of the aforementioned three stability criteria for a patient at least once the stability

compliance assessment is not "No presence of fluid and BCVA stable and retinal thickness stable" (criterion 1 mentioned above)

The following OCT variables: CSRT, FCP thickness will be adjusted based on the OCT device used according to the correction factors outlined in Table 2-1.

Table 2-1 OCT correction factors

Variables	OCT device	Correction factor
CSRT (µm)	Heidelberg Spectralis	No correction required
	Cirrus Zeiss*	Add 56,29 µm to unadjusted value
	Topcon	Add 121,72 µm to unadjusted value
	Other **	No correction required
	NA **	No correction required
FCP thickness (µm)	Heidelberg Spectralis	No correction required
	Cirrus Zeiss*	Add 28,3 µm to unadjusted value
	Topcon	No correction required
	Other **	No correction required
	NA **	No correction required

* The Cirrus Zeiss OCT device refers to Cirrus Zeiss Macular Cube 512 x 128 x 1024.
** A correction factor is not applicable in this case.

2.2 Analysis sets

The **Randomized Set (RS)** will consist of all patients who were randomized to one of the treatment arms and who received at least one application of study treatment.

The **Full Analysis Set (FAS)** will consist of all patients as randomized who received at least one application of study treatment and have at least one post-baseline assessment for the primary endpoint (BCVA). Following the intent-to-treat principle, patients will be analyzed according to the treatment assigned. No data will be excluded from the FAS analyses because of PDs.

The **Per Protocol Set (PPS)** will consist of all patients in the FAS who received study treatment as randomized and completed the treatment phase of the trial without major PDs.

Criteria that are assumed to impact the PPS will be defined in the data review plan (DRP), data handling plan (DHP), and Blind Data Review Meeting (BDRM) before DBL.

The **Safety Set** will consist of all patients from the RS who had at least one post-baseline safety assessment. Patients will be analyzed according to treatment received. The statement that a patient had no AEs also constitutes a safety assessment.

For rules of exclusion criteria of analysis sets refer to Appendix 5.3.

Table 2-2 Analysis data sets for specific outputs

	All screened patients	RS	FAS	PPS	Safety Set
Screening failures	X				
Demographics and baseline characteristics			X		
Analysis sets		X			
Patient disposition	X	X			
Number of patients by visit		X			
Protocol deviations		X			
Medical history			X		
Concomitant medication					X
Primary and key secondary efficacy variables			X	X	
Other efficacy analyses			X		
Patient reported outcomes			X		
Safety analyses					X
Exposure					X
Subgroup analyses			X		
Non-inferiority analyses			X	X	

The number and percentage of patients in each analysis set will be summarized based on the RS.

2.2.1 Subgroup of interest

Gender subgroup analysis will be done for the primary objective.

For patients with [redacted], for patients that needed additional panretinal photocoagulation (PRP) treatment and for patients experiencing an incident leading to vitrectomy (see Section 2.1.1 for definition of the subgroups of interest), separate subgroup analysis will be presented using the endpoints:

- BCVA changes in ETDRS letters from baseline to month 12
- Number of visits and treatments
- Progression/ regression of neovascularization from baseline to month 12 (i.e. change in PDR in the study eye from baseline to month 12)
- Changes in CSRT from baseline to month 12 at each visit

Patients with missing baseline values used to define the subgroups will be presented in a category “unknown” in the respective subgroup analyses.

2.3 Visit windowing

2.3.1 Visits

Visit windowing will be performed for all post-baseline visits collected in the database where the patients have more than one post-baseline visit assessment which will be summarized by visit. The screening and baseline visits will not be remapped. The study day for each visit will be derived (see Section 2.1.1 for definition); this day will be then be used to determine the actual visit based on the visit windows outlined in Table 2-3.

As it is planned to have both end of treatment (EoT) and EoS analyses for certain assessments, respective flags will be created for the assessments of interest. The EoT flag will flag all values which occur up and including EoT while the EoS flag will flag all values collected. If more than one remapped visit occurs at a visit, only one will be selected for summary tables but all visits will be listed. Therefore two additional variables will be created which will indicate which values will be used for analysis purposes for EoT and EoS analyses respectively. If more than one remapped post-baseline value for the respective analyses occurs at a visit, only the value closest to the target study day will be selected (see Section 2.1.1 for definition). If there are two observations which have the same difference in days to the target day or if there are two observations on the same day, the first value will be used.

Table 2-3 Visit windows (monthly)

Post-baseline timepoint	Visit timepoint (monthly)	Target Study day	Visit window (study days)
3	Month 1	30	2 to 44
4	Month 2	60	45 to 74
5	Month 3	90	75 to 104
6	Month 4	120	105 to 134
7	Month 5	150	135 to 164
8	Month 6	180	165 to 194
9	Month 7	210	195 to 224
10	Month 8	240	225 to 254
11	Month 9	270	255 to 284
12	Month 10	300	285 to 314
13	Month 11	330	315 to 344
14	Month 12	360	>=345

2.3.2 Unscheduled visits

All data collected at unscheduled visits will at a minimum be listed.

All safety and exposure to study treatment data collected at unscheduled visits will be used.

2.4 Patient disposition, demographics and other baseline characteristics

Demographics, baseline ocular and non-ocular characteristics will be summarized and listed for the FAS for each randomized treatment arm and overall, unless specified otherwise.

No inferential statistical analysis will be performed on these characteristics.

2.4.1 Patient disposition

The number and percentage of patients who are screening failures and the reason for screening failure will be presented for all patients screened.

Patient disposition will be summarized for all patients by treatment arm and overall. The number and percentage of patients who completed the study, who discontinued the study early, and also who prematurely discontinued treatment but remained in the study will be displayed.

For those who discontinued the study early or who discontinued the investigational study treatment prematurely but remained in the study, the primary reason for study or investigational study treatment discontinuation will be summarized.

Study completion and investigational study treatment completion will also be summarized by the visit of study termination/ completion and study treatment discontinuation/ completion, respectively.

The number and percentage of patients attending each visit will also be presented by treatment arm.

Furthermore, disposition will be presented in by-patient listings. A study milestones listing will also be provided containing first patient first visit (FPFV), last patient last visit (LPLV) and the trial duration (the time period between FPFV and LPLV), overall and by site.

2.4.2 Protocol deviations

PD severity and impact on analysis populations can be found in the DRP and DHP, these are subject to change however and the final definitions and list of PDs will be documented during the BDRM. The PDs are used in excluding entire patients or particular data within a patient from relevant analysis sets. Criteria defining PDs are outlined in the Appendix 5.3.

All PDs will be summarized through presenting the number and percentage of patients with each deviation by treatment arm and total.

Patients with multiple PDs will only be counted once at each level of summarization.

Additionally all relevant (according to medical review) reportable protocol deviations will be summarized under the following deviation categories used in the DRP and DHP. Currently these are:

- Patient did not satisfy relevant inclusion criteria (I)
- Patient met relevant exclusion criteria (E)
- Patient received the wrong treatment or incorrect dose (S)
- Patient developed withdrawal criteria during the study, but not withdrawn (D)

- Patient took an excluded concomitant medication (M)
- Others (O)

In addition, a listing of PDs will be produced including the date and study day of the deviation occurrence with the accompanying deviation code and severity.

2.4.3 Background and demographic characteristics

Demographics and baseline data will be summarized and listed for the FAS by treatment arm and overall, unless specified otherwise. Descriptive statistics will be provided for the below demographics and baseline characteristics:

Demographics

Continuous variables:

- Age (years)

Categorical variables:

- Age group (<65, >=65 years)
- Sex (Male, Female)
- Race (Caucasian, Black, Asian, Other)

Non-ocular baseline characteristics

Continuous variables:

- Vital signs (height [cm], weight [kg], pulse [bpm], systolic and diastolic blood pressure [mmHg])
- Body mass index (BMI) (kg/m^2)
- HbA1c (%)
- Serum Lipid Levels (Cholesterol, HDL-Cholesterol, LDL-Cholesterol, Triglycerides) (mg/dL)
- Estimated number of cigarette pack years
- Time since smoking termination (years)
  - Note: Time since smoking termination is only completed for ex-smokers.
- Time since first diagnosis of diabetes (years)

[redacted]

Categorical variables:

- Pregnancy testing for women of child-bearing potential (Negative, Positive)
- Smoking history (Never smoked, Current smoker, Ex-smoker)
- Time since smoking termination group (< 2, 2 to < 10, 10 to < 20, >= 20 years)
  - Note: Time since smoking termination is only completed for ex-smokers.
- Diabetes type (Type I, Type II)

- Time since first diagnosis of diabetes group (< 2, 2 to < 10, 10 to < 15, 15 to < 20, >= 20 years)

Ocular baseline characteristics

Continuous variables:

- Time since first diagnosis of DME (years) (study eye, fellow eye)
- BCVA (letters) (study eye, fellow eye)
- Intraocular pressure (mmHg) (study eye, fellow eye)
- [redacted]

Categorical variables:

- Time since first diagnosis of DME group (< 2, 2 to < 10, 10 to < 15, 15 to < 20, >= 20 years) (study eye, fellow eye)
- Study eye selection (Left, Right) (study eye)
- [redacted]

The following assessments presenting retinal characteristics are provided by the CRC.

OCT baseline characteristics (from CRC)

Continuous variables:

- CSRT (µm) (study eye)
- [redacted]
- FCP thickness (µm) (study eye)
- [redacted]

Categorical variables:

- [redacted]

- Automated segmentation of CSRT (Correct, Error manually corrected, Manual correction too time-consuming, Not gradable, NA) (study eye)
- [redacted]
- CSRT >=300 µm (Yes, No, Not gradable, NA) (study eye)
- [redacted]
- Automated or manually corrected segmentation of CSRT by OCT software (Correct, Manually measured, Not gradable, NA) (study eye)
- [redacted]

Note: The descriptive statistics summary table and listing for OCT baseline characteristics will also be produced using the unadjusted CSRT and FCP thickness values.

Color Fundus Photography (CFP) baseline characteristics (from CRC)

The following variables will only be listed by treatment arm.

Categorical variables:

- CFP modality available? (Yes - Required; Yes - Not required; No – Required; No - Not required)
- CFP quality OD (Excellent, Good, Adequate, Poor, NA)
- CFP quality OS (Excellent, Good, Adequate, Poor, NA)
- CFP submission acceptance (Completely acceptable, Acceptable with remarks, Not acceptable, NA)

DRS baseline characteristics (from CRC)

Categorical variables:

- DRS (Mild*NPDR, Moderate*NPDR, Severe*NPDR, Proliferative Diabetic Retinopathy, Status post panretinal laser coagulation - not gradable, NA) (study eye, fellow eye)

General image grading characteristics (from CRC)

Categorical variables:

- Confirmed eligibility of study eye (Yes, No, NA)
- Concerns for fellow eye to be considered as study eye alternatively at screening (Yes, No, NA)
- Adequacy of image quality for eligibility (Yes, No, Questionable, Not gradable, NA)
- Presence of any diabetic macular edema (Yes, No, Questionable, Not gradable, NA) (study eye)
- No presence of concomitant conditions that would prevent improvement (Yes, No, Questionable, Not gradable, NA) (study eye)
- No presence of structural damage in the center of the macula (Yes, No, Questionable, Not gradable, NA) (study eye)
- No presence of vitreous hemorrhage impairing the adequate diagnosis (Yes, No, Questionable, Not gradable, NA) (study eye)
- No presence of relevant vitreofoveal adhesion or epiretinal membrane with foveal involvement (Yes, No, Questionable, Not gradable, NA) (study eye)
- No presence of proliferative vitreoretinopathy (Yes, No, Questionable, Not gradable, NA) (study eye)
- No presence of central retinal neovascularizations (Yes, No, Questionable, Not gradable, NA) (study eye)
- Presence of signs of vitreous hemorrhage (Yes, No, Questionable, Not gradable, NA) (study eye, fellow eye)

- Presence of signs of panretinal laser coagulation (Yes, No, Questionable, Not gradable, NA) (study eye, fellow eye)
- Presence of signs of laser treatment of the macula (Yes, No, Questionable, Not gradable, NA) (study eye, fellow eye)
- Lens status (Phakic, no marked opacity; Phakic, marked opacities; Pseudophakic; Aphakic; Other; Not gradable; NA) (study eye, fellow eye)
- Capillary non-perfusion – general (Yes, No, Questionable, Not gradable, NA) (study eye, fellow eye)
- Capillary non-perfusion – involvement of center (Yes, No, Questionable, Not gradable, NA) (study eye, fellow eye)
- Capillary non-perfusion – area extent (≤ 3 PD, > 3 PD ≤ 5 PD, > 5 PD ≤ 7 PD, > 7 PD ≤ 10 PD, > 10 PD, NA) (study eye, fellow eye)

The following ocular assessments (confocal scanning laser ophthalmoscope [cSLO]) are optional. They will only be performed for patients with the respective additional informed consent in participating centers equipped with the respective device.

cSLO baseline characteristics (from CRC)

Categorical variables:

- cSLO modality available? (Yes - Required; Yes - Not required; No – Required; No - Not required)
- IR image quality (Excellent, Good, Adequate, Poor, NA)
- Multicolor quality (Excellent, Good, Adequate, Poor, NA)
- FAF quality (Excellent, Good, Adequate, Poor, NA)
- cSLO submission acceptance (Completely acceptable, Acceptable with remarks, Not acceptable; NA)

2.4.4 Medical history

The number and percentage of patients from the FAS with relevant medical history (ocular and non-ocular) and current medical conditions will be tabulated by system organ class (SOC) and PT of the current Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 19.1 or higher). The SOCs will be presented in alphabetical order. PTs will be ordered by treatment arm and total by decreasing proportion in the total group.

Separate summaries will be presented for histories and current medical conditions (documented in the database as still active at the start of the study). Additionally, these tables

will be provided separately for ocular (presented for both eyes in addition to study eye and fellow eye separately) and non-ocular histories and conditions.

For handling of missing or incomplete start and end dates, see Appendix 5.1.3 of this document.

Additionally all information will be listed including the investigator reported term and the diagnosis/ surgery date and day.

2.5 Treatments (study treatment, concomitant therapies, compliance)

Summaries will be presented for the Safety Set. All analyses will be presented for the study eye only, unless specified otherwise.

The fellow eye is not treated with investigational study treatment and will therefore not be applicable for Section 2.5.1.

2.5.1 Study treatment/ compliance

2.5.1.1 Investigational treatment

Descriptive statistics for the total number of ranibizumab injections will be presented for each treatment phase separately and overall by treatment group and total. Summary statistics for the number of injections per patient will be presented by frequency distribution (number of patients with 1 injection, number of patients with 2 injections, on up to the maximum number of injections for any one patient) for the given treatment phase and overall, and cumulatively.

Descriptive statistics will also be provided by treatment arm and total for:

- duration of the overall study period
- duration of the initial treatment phase
- duration of the maintenance phase
- duration of time between visits (overall and for maintenance phase)
- duration of time between injections (overall and for maintenance phase)

This table will also be repeated by actual treatment strategy. Furthermore, duration of time between visits and duration of time between injections will be presented overall and by actual treatment strategy from month 4 onwards

At each visit, the number and percentage of patients receiving or not receiving a ranibizumab injection will be summarized from baseline to month 11. Additionally, the reasons for no study treatment given will be summarized. This will include details for disease activity as recorded in the Ranibizumab dose administration eCRF (no disease activity, disease activity stable with maximum BCVA, BCVA and disease activity stable, Adverse event or disease activity present but patient refused additional study treatment). The denominator at each visit will be the number of patients for which a study treatment decision was recorded in the eCRF at that visit.

A frequency table will be presented at each visit showing the number and percentage of patients for overall and each individual stability compliance assessment category (see Section 2.1.1 for definition of the stability compliance assessment) who stopped treatment due to one of the following three stability criteria:

- No disease activity (BCVA maximum, CRT minimum and no further signs of activity in morphologic parameters)
- Disease activity stable with maximum BCVA (no further improvement of other morphologic parameters)
- BCVA and disease activity stable (no further improvement of BCVA and other morphologic parameters).

By-patient listings for ranibizumab injection administration will be provided.

Descriptive statistics presenting the total number of cases (patient and event counts) where patients were treated not in line with the stability compliance assessment (see Section 2.1.1 for definition of such patients) and the frequency distribution (number of patients treated in line with the stability compliance assessment, number of patients treated once not in line with the stability compliance assessment, number of patients treated twice not in line with the stability compliance assessment, on up to the maximum number of cases where patients were treated not in line with the stability compliance assessment for any one patient) will be presented for the maintenance phase by treatment arm and total. Alignment with the stability compliance assessment (Yes, No) will be included in the ranibizumab injection administration by-patient listing.

Descriptive statistics will be provided for the duration of:

- study observation period (Date of last visit – Date of first administration of study treatment + 1 day)
- study treatment period (Date of last administration of study treatment – Date of first administration of study treatment + 1 day).

The duration will be categorized into periods of 30 days. Descriptive statistics for the duration of study treatment period will also be provided by overall stability compliance assessment (refer to Section 2.1.1 for definition).

The number and percentage of patients for whom the visit interval was increased, kept or reduced will be summarized by visit. Additionally, the reasons for increasing, reducing, or keeping the visit interval the same, as recorded in the Visit Interval eCRF will be listed. This listing will be repeated for those patients with a treatment pattern which includes X (see Section 2.5.1.1.1 for definition), the listing will also include the visit structure and associated visit dates.

The source of confirmation of disease activity as provided in the eCRF (BCVA, OCT, Ophthalmoscopy, CFP, FA, Other) will be also be listed.

2.5.1.1.1 Investigational treatment pattern

The pattern of ranibizumab treatment administrations will be summarized for both treatment arms from baseline to month 12. For a given patient, the pattern of ranibizumab treatments will be identified by a series of numbers or letters as defined below:

- T indicates EoT visit (only for patients who discontinue treatment early but stay in the study)
- S indicates EoS visit

- X indicates an extended interval where no visit was required in the maintenance phase for a patient due to DI with an actual treatment strategy of Dynamic PRN or Treat & Extend
- M indicates that the patient missed the visit
- 0 indicates that a patient attended the scheduled visit at which study treatment was not given
- 1 indicates that a patient attended the scheduled visit at which study treatment was given
- F indicates a follow-up visit after EoT without further treatment

For example, if a patient received injections at baseline, months 1 to 5, 8 and 10, attended the visit at months 6 and 7 but was not treated in the study eye, missed month 9, discontinued prior to month 12, the ranibizumab treatment pattern for that patient would be 111111001M1S.

Investigational treatment patterns will be listed for all patients.

2.5.1.1.2 Re-treatments

The definition of re-treatment is provided in Section 2.1.1.

Descriptive statistics for the number of ranibizumab re-treatments during the maintenance phase and the frequency distribution (number of patients without any re-treatment, number of patients with 1 re-treatment, on up to the maximum number of re-treatments for any one patient) will be presented by treatment arm and total. Re-treatment will only be derived for those patients with a completed initial treatment phase.

The time to first ranibizumab re-treatment (in days) during the maintenance phase will be calculated as the period between the date of the first injection (YES treatment given) in the maintenance phase and the date of the start of the maintenance phase (NO treatment given when the reason is one of the three stability criteria, as defined in Section 2.1.1) + 1 day.

Note: If a patient had no treatment at month 3, missed month 4 and received treatment at month 5 then we can assume that the duration of each month is 30 days; hence time to re-treatment would be 30 + 1 days.

Kaplan-Meier (KM) curves and descriptive statistics will be provided for time to re-treatment. The main focus of this study is to understand the effect of the two treatments of interest. Therefore, time to first re-treatment during the maintenance phase will be derived for:

1. up to EoT
   This means:
   - if a patient prematurely discontinues treatment (EoT) but stays in the study longer (EoS > EoT), then only data up to EoT will be used for calculation and censoring
   - if a patient prematurely discontinues treatment and the study at the same time, then data up to EoS will be used for calculation and censoring
   - if a patient does not discontinue treatment early, then data up to EoS will be used for calculation and censoring

2. up to EoS
   In case of no ranibizumab re-treatment, the duration will be censored at EoS.

In addition, time to first re-treatment during the maintenance phase will be derived excluding those patients who discontinue treatment early but stay in the study.

The number and percentage of patients experiencing re-treatments during the maintenance phase, together with defined reason for re-treatments, will be displayed by visit.

In addition, descriptive statistics for duration of TFI will be provided by treatment arm and total. A frequency table for the number of TFIs experienced will also be presented.

The proportion of patients with a TFI during the maintenance phase of at least 3 months will be also be summarized by treatment arm and total.

2.5.1.2 Laser Photocoagulation

Different types of laser treatments and regimes can be applied in addition to study treatment to the patients in both arms:

- Focal
- Grid
- Panretinal
- Focal + Grid
- Panretinal + Focal + Grid
- Other

The number of laser treatments up to month 12 will be presented for both treatment arms by frequency distribution (number of patients with no laser treatments, number of patients with 1 laser treatment, on up to the maximum number of laser treatments for any one patient) and cumulatively. Summaries will be presented separately for the different types of laser treatment (see Section 2.1.1).

Summary tables with the number and percentage of patients who received laser treatment or not and the reason for laser treatment as stated in eCRF will be given by visit.

By-patient listings for laser photocoagulation will be provided.

2.5.2 Prior and concomitant therapies

The number and percentage of patients taking concomitant therapies will be summarized by PT according to the WHO Drug Reference List dictionary (version 15.3 or higher). Summaries of the following will be presented by treatment arm:

- Prior therapies: therapies received prior to the start of study treatment (therapy end date prior to date of first administration of any study treatment)
- Concomitant therapies: therapies received on/ after the start of study treatment (therapy end date on or after the date of first administration of any study treatment)
  Note: Therapies which started prior to the start of study treatment but continued into the treatment period will be classified as concomitant.

For both, prior and concomitant therapies, summary tables will be presented for ocular therapies (for both eyes in addition to study eye and fellow eye separately) and non-ocular therapies.

Concomitant medications as well as significant non-drug therapies that are prohibited as per protocol and given during the conduct of the study while on study treatment will be provided in separate tables. These patients will be identified using the PD M06 (see Appendix 5.3 for details on this PD) and the prohibited medications and significant non-drug therapies will be identified by the medical advisor during the BDRM.

For those patients who discontinued the investigational study treatment prematurely but remained in the study, summary tables will be presented for concomitant ocular therapies (for both eyes in addition to study eye and fellow eye separately) and non-ocular therapies that were received after the EoT visit.

For handling of missing or incomplete start and end dates, see Appendix 5.1.2 of this document.

By-patient listings for prior and concomitant therapies will be provided.

2.6 Analysis of the primary objective

The primary objective is to demonstrate that the mean average change of BCVA, averaged over all post-baseline visits to month 12, in patients with DME treated with ranibizumab injections at the discretion of the investigator (DI) and in accordance with disease activity criteria is non-inferior to current standard of care (PRN).

The main focus of this study is to understand the effect of the two treatments of interest. Therefore, data from baseline to EoT will be used for primary objective analyses, unless specified otherwise. This means:

- if a patient prematurely discontinues treatment (EoT) but stays in the study longer (EoS is after EoT), then only data up to EoT will be used
- if a patient prematurely discontinues treatment and the study at the same time, then data up to EoS will be used
- if a patient does not discontinue treatment early, then data up to EoS will be used.

In the cases where patients discontinued study treatment early but continued in the study, further sensitivity analysis using any BCVA data collected after treatment ended until the patient completed the study will be presented as defined in Section 2.6.4.

Only the study eye will be evaluated for efficacy.

2.6.1 Primary endpoint

The primary efficacy variable of this study is the mean average change from baseline in BCVA over the 12-month treatment period. This is defined as the difference between the average level of BCVA (ETDRS letters) over all post-baseline assessments from month 1 to month 12 (or premature discontinuation if earlier) and the baseline level of BCVA. Average change from baseline in BCVA will henceforth be referred to as visit-averaged change from

baseline in BCVA. Therefore the primary efficacy variable of this study is the mean visit-averaged change from baseline in BCVA from month 1 to EoT.

That is, if BCVA0, BCVA1, BCVA2, ⋯, and BCVA12 define BCVA measurements at baseline, month 1, month 2, ⋯, and month 12, respectively, then the primary efficacy variable D0 is derived as:

$D0 = [(BCVA1 + BCVA2 + \cdots + BCVA12)/12] - BCVA0$

The primary analysis will be performed after all patients have completed the month 12 visit (or discontinued the study prematurely before month 12) using the FAS based on the Last Observation Carried Forward (LOCF).

2.6.2 Statistical hypothesis, model, and method of analysis

As a consequence of the early recruitment termination, all analyses will be interpreted in a purely descriptive manner. Nevertheless, the planned non-inferiority hypothesis testing of the ranibizumab injections at the discretion of the investigator (DI) and ranibizumab injections of current standard care (PRN) for patients with DME will still be performed.

The following hypotheses related to non-inferiority at a one-sided 0.025 significance level will be performed:

Null hypothesis: H_0: $\mu_{DI} - \mu_{PRN} \leq -\Delta$

Alternative hypothesis: H_A: $\mu_{DI} - \mu_{PRN} > -\Delta$

where μ_{DI} and μ_{PRN} are the unknown mean visit-averaged change from baseline in BCVA from month 1 to EoT, in the DI regimen and the PRN regimen, respectively. Δ is the non-inferiority margin and is predefined to be 4 letters. The hypothesis testing with respect to non-inferiority of BCVA will be carried out using an analysis of covariance (ANCOVA) model including study treatment (DI, PRN) and center as factors and baseline BCVA as continuous covariate.

The Least Square (LS) ("adjusted") means for each treatment arm and estimates of the difference (DI - PRN) will be given along with the respective two-sided, 95% CI and the p-value for the (unshifted) null hypothesis ($\mu_{DI} - \mu_{PRN} = 0$).

The one-sided non-inferiority p-value for the shifted hypothesis ($\mu_{DI} - \mu_{PRN} \leq -\Delta$) will be calculated. Non-inferiority will be claimed, if the lower limit of the two-sided 95% CI (equivalent to the one-sided 97.5% CI) does not exceed $-\Delta$ (i.e. -4 letters).

There are no multiplicity issues as there is only one primary comparison.

The key assumptions that underlie the use of ANCOVA model for the primary analysis will be checked. The normality assumption of the error term will be performed and in case of clear deviations, a non-parametric comparison – Wilcoxon Rank Sum Test – will be performed instead of ANCOVA for the primary analyses. Homogeneity of variance between/ among treatment arms will be evaluated visually.

At each visit, descriptive statistics will be provided for the following values of the primary efficacy variable BCVA by visits and treatment arms:

- Baseline
- Absolute and change from baseline
- Visit-averaged change from baseline in BCVA from month 1 to EoT

Moreover, the course over time for the absolute values and for changes from baseline for BCVA variable will be presented graphically for both treatment arms, showing the mean and SD of the mean per visit.

Individual BCVA level profiles will be listed.

2.6.3 Handling of missing values/censoring/discontinuations

For the FAS, the analysis will follow a LOCF approach with the specification that monotone missing values will be replaced by the last post-baseline observation prior to the missing timepoint. Intermittent missing values will be replaced by the mean of the closest non-missing adjacent values.

2.6.4 Supportive analyses

For supportive and sensitivity analyses of the primary analysis where p-values are presented, the one-sided non-inferiority p-value for the shifted hypothesis ($\mu_{DI} - \mu_{PRN} \leq - \Delta$) will also be provided in addition to the p-value for the (unshifted) null hypothesis.

The primary analysis will be repeated for the PPS (LOCF) using the same methodology as outlined in Section 2.6.2. Since this is a non-inferiority trial, the corresponding results obtained for the PPS are regarded as of almost equal importance for the interpretation. Any major discrepancies in the results across analyses will be investigated as necessary.

The same model as the one used for the primary analysis will be repeated for the FAS on observed data (as observed) as well as PPS (as observed). The primary efficacy variable D0 will be calculated as follows:

D0 = [(sum of non-missing BCVA1, BCVA2, ⋯ BCVA12 values) /k] - BCVA0

where k (k = 1, ⋯,12) is the number of non-missing BCVA values between month 1 and month 12, inclusively, and BCVA0, BCVA1, ⋯ BCVA12 are as defined in Section 2.6.1.

Furthermore, the mean visit-averaged change from baseline in BCVA from month 1 to EoT, will be compared between the two treatments based on the assumption of a “Missing at Random (MAR)” process, i.e. assuming that the statistical behavior of a patient who drops out post-withdrawal is the same as that for a patient remaining in the study and sharing the same covariates and the same measurement history. This analysis will be based on a mixed model repeated measurement (MMRM). The MMRM model will be fit to all the BCVA data collected from month 1 to month 12 inclusive. The MMRM analysis will include subject as a random effect, and the following as effects:

Categorical variables

- treatment
- center

- visit

Continuous variables

- baseline BCVA

Interactions

- treatment by visit interaction
- visit by baseline BCVA interaction

A term for visit will be included in the repeated statement and an unstructured correlation matrix will be used thus allowing adjustment for correlations between time points within patients. A Kenward-Roger approximation will be used for the denominator degrees of freedom.

If the model with the unstructured correlation matrix fails to converge then the following correlation structures should be fitted; variance components, compound symmetry, first order autoregressive and Toeplitz. The value of the Akaike Information Criteria (AIC) should be considered to choose the most appropriate model. Note that, other things being equal, the model with the smallest AIC is preferred. In case of inadequate results, further modification of the model may be required.

Additional sensitivity analyses of the primary analysis (using the same methodology as outlined in Section 2.6) for FAS (LOCF) will be performed:

- using all data from baseline to EoS (visit-averaged change from baseline in BCVA from month 1 to EoS).

  This analysis is meant to additionally include the data collected between EoT and EoS for those patients who prematurely discontinue from treatment but stay in the study.
- excluding patients who discontinue treatment early but stay in the study
- using all data for patients who reach month 12 (i.e. completers, patients who do not prematurely discontinue treatment or the study early)

The LS (“adjusted”) means for each treatment arm and estimates of the difference (DI - PRN) will be given along with the respective two-sided, 95% CI. P-values will be presented for the treatment difference.

The difference in treatment effects will be illustrated graphically using a forest plot for each analyzed population for the primary analysis and each sensitivity and supportive analysis: the estimates of differences in visit-averaged change from baseline in BCVA from month 1 to the timepoint of interest, between the two treatment arms will be presented along with respective two-sided 95% CIs.

Furthermore, a frequency table presenting the number and percentage of patients based on FAS (LOCF) with a change of 5, 10, or 15 letters in BCVA from baseline at Month 12 will be provided.

KM curves and descriptive statistics will be provided for time to:

- first gain in BCVA from baseline of >=10 letters
- first gain BCVA from baseline of >=15 letters

for the FAS. The main focus of this study is to understand the effect of the two treatments of interest. Therefore, time to first gain >= x letters (where x=10 or 15 letters) will be derived for:

1. up to EoT
   This means:
   - if a patient prematurely discontinues treatment (EoT) but stays in the study longer (EoS > EoT), then only data up to EoT will be used for calculation and censoring
   - if a patient prematurely discontinues treatment and the study at the same time, then data up to EoS will be used for calculation and censoring
   - if a patient does not discontinue treatment early, then data up to EoS will be used for calculation and censoring
2. up to EoS
   In case of no gain of post-baseline BCVA >= x letters (where x=10 or 15 letters), the duration will be censored at EoS.

The number and percentage of FAS patients with the aforementioned gain categorizations after their first three ranibizumab injections (i.e. change of 5, 10, or 15 letters in BCVA from after their first three ranibizumab injections at Month 12) will also be presented.

Descriptive statistics will be produced for the baseline values, absolute values, and the change from baseline values to month 12 by overall stability compliance assessment (refer to Section 2.1.1 for definition). In addition, descriptive statistics will be provided for the visit-averaged change from baseline in BCVA from month 1 to EoT (primary outcome) by overall stability compliance assessment for the total (not by treatment arm).

Additionally, gender subgroup analysis will be done for the primary analysis (based on FAS [LOCF]). Descriptive statistics will be provided for the visit-averaged change from baseline in BCVA from month 1 to EoT (primary outcome) for patients with the following characteristics (see Section 2.1.1 for definitions of these characteristics):

- [redacted]
- the need of additional PRP treatment
- experiencing an incident leading to vitrectomy

2.7 Analysis of the key secondary objective

There are no key secondary objectives in this study.

2.8 Analysis of secondary efficacy objectives

The analysis of the secondary efficacy objectives will focus on the study eye only and it will be based on the FAS (LOCF), unless otherwise specified. Only data from baseline to EoT will be used for secondary objective analyses, unless specified otherwise. This means:

- if a patient prematurely discontinues treatment (EoT) but stays in the study longer (EoS is after EoT), then only data up to EoT will be used
- if a patient prematurely discontinues treatment and the study at the same time, then data up to EoS will be used
- if a patient does not discontinue treatment early, then data up to EoS will be used.

2.8.1 Secondary endpoints

The following secondary efficacy endpoints will be evaluated:

- Change of BCVA in ETDRS letters from baseline to month 12
- Number of visits, injections and TFIs
- Change of CSRT (µm) from baseline to month 12
- Change in FCP thickness (µm) from baseline to month 12
- Change in 0, 1, 2 or more steps in DRS from baseline to month 12
- ANCOVA analysis of primary outcome with the additional covariates: relevant changes of HbA1c, blood pressure (systolic, diastolic), and lipid levels (cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides)

Changes in CSRT and FCP thickness will be evaluated by the CRC assessing OCT images. Changes in DRS will be evaluated by the CRC scoring CF Photography and FA images and will be defined in 5 severity levels:

1. Mild non-proliferative retinopathy (NPDR)
2. Moderate NPDR
3. Severe NPDR
4. Proliferative DR
5. Status post panretinal laser coagulation - not gradable

2.8.2 Statistical hypothesis, model, and method of analysis

Similar to the primary analysis, the secondary analysis will be interpreted in a purely descriptive manner due to the reduced sample size although hypothesis testing will still be performed for the specific secondary objectives.

For the continuous secondary endpoints BCVA change from baseline, CSRT change from baseline, and FCP thickness change from baseline, summary statistics will be produced for the baseline values, absolute values and the change from baseline values to month 12. The summary statistics for the baseline values, absolute values and the change from baseline values to month 12 will also be produced using the unadjusted CSRT and FCP thickness values. The course over time for the absolute values and for changes from baseline will be presented graphically for the treatment arms for CSRT and FCP thickness variables, showing the mean and SD per visit.

Tests comparing the changes in BCVA, CSRT and FCP thickness will be based on ANCOVA models, containing the baseline values of the dependent variables as continuous covariates, and center and treatment as categorical covariates. The LS (“adjusted”) means for each treatment arm and estimates of the difference (DI - PRN) will be given along with the respective two-sided, 95% CI. Two-sided p-values will be presented for the treatment difference.

Additional sensitivity analyses of changes in BCVA and CSRT will be performed using all data from baseline to EoS. These sensitivity analyses will include descriptive analyses and a repeat of the ANCOVA outlined in the previous paragraph.

The total number of injections will be summarized as described in Section 2.5.1.1. Additionally, the total number of visits and total number of TFIs (see Section 2.1.1 for definition of TFI) to month 12 will be summarized for the two treatment arms descriptively. Note: All data up to EoS will be used for FAS.

Change in DRS from baseline to month 12 (improvement of 0, 1, 2, and > 2, steps, or loss of 1, 2, > 2 steps) will be summarized by presenting the number and percentage of patients in each treatment arm achieving the endpoint for FAS (LOCF). This improvement/ loss will only be derived for those patients with a DRS score of 1, 2, 3, or 4 at baseline and at month 12. In addition, a shift table will be produced to summarize the shift from baseline to month 12 in DRS score for FAS (LOCF).

Additional ANCOVA models for the primary outcome (visit-averaged change from baseline in BCVA from month 1 to EoT) will be performed with the following extra binary covariates (Yes, No):

- relevant changes of HbA1c (defined as any change of HbA1c (%) from baseline of > 1%)
- relevant changes of systolic blood pressure (defined as any change of systolic blood pressure (mmHg) from baseline > 30)
- relevant changes of diastolic blood pressure (defined as any change of diastolic blood pressure (mmHg) from baseline > 20)
- relevant changes of cholesterol (defined as any change in cholesterol from baseline of (1) for female: <= 2.38 mmol/l; 92 mg/dl or >= 6.06 mmol/l; 234 mg/dl, (2) for male: <=2.12 mmol/l; 82 mg/dl or >= 4.97 mmol/l; 192 mg/dl)
- relevant changes of HDL-cholesterol (defined as any change in HDL-cholesterol from baseline of <= 1.04 mmol/l; 40 mg/dl)
- relevant changes of LDL-cholesterol (defined as any change in LDL-cholesterol from baseline of >= 3.38 mmol/l; 130 mg/dl)
- relevant changes of triglycerides (defined as any change in triglycerides from baseline of >= 1.71 mmol/l; 150 mg/dl)

For each ANCOVA model, the LS (“adjusted”) means for each treatment arm and estimates of the difference (DI - PRN) will be given along with the respective two-sided, 95% CI together with two-sided p-values. In order to derive the final ANCOVA model, the following steps will be used:

1. The importance of the individual dependent variables on the primary outcome response variable will be testing using the primary ANCOVA model (see Section 2.6.2 for details) for FAS (LOCF). Inclusion in the primary ANCOVA model when $p < 0.2$.
2. The backward stepwise regression procedure will be used to choose the optimal set of dependent variables from the set of statistically significant dependent variables tested in step 1. The significance level to stay in the ANCOVA model is $p < 0.05$.

Note: In case of inadequate results, further modification of the model may be required.

2.8.3 Handling of missing values/censoring/discontinuations

For certain secondary endpoints where specified, the analysis will follow a LOCF approach (see Section 2.6.3 for details).

Otherwise the analysis will follow FAS as observed approach. Thus no imputation for missing values will be performed.

2.9 Safety analyses

Safety parameters will include AEs, intraocular pressure (IOP), vital signs, and laboratory results. All safety analyses will be performed using the Safety Set. Patients will be analyzed according to treatment received. No missing data will be imputed for safety analyses.

2.9.1 Adverse events

AEs will be deemed treatment emergent if the onset date is on or after the date of first treatment with investigational drug. Any AEs recorded prior to the start of investigational drug will be listed together with all other AEs. Only TEAEs will be summarized. If any event has an incomplete onset date, this will be handled as described in the Appendix 5.1.1.

The period for observing TEAEs for the study eye begins at the first administration of study treatment. This safety observation period (days) for the study is defined as: (date of last administration of investigational study treatment - date of first administration of study drug) + 31 (i.e. 30 days after last administration of investigational study treatment).

TEAEs will be presented for both eyes in addition to the study eye and fellow (untreated) eye separately. AEs will be summarized by presenting for each treatment arm and total the number and percentage of patients having any AE (patient counts). Note: The overall TEAE summary table will in addition include the number of AEs within each category (event counts). AEs will be analyzed separately for ocular and non-ocular AEs (according to the

investigator's response to site on the AE eCRF form). Patients who experienced multiple AEs for a PT will be counted once, similarly for patients with multiple AEs per SOC. The SOCs will be presented in alphabetical order. PTs will be ordered within each SOC for both treatment arms and total by decreasing incidence in the total group.

Ocular AEs will be presented separately for the study eye, fellow eye and both eyes. Ocular AEs that were recorded in both eyes will be reported for both eyes and additionally separately for each eye.

AEs that were suspected to be related to study drug or procedures based on the investigator's decision will be summarized. The maximum severity of all TEAEs during the study (safety observation period) will be summarized. Summary tables will also be presented for the subset of AEs suspected to be treatment related.

Deaths, serious adverse events (SAEs), and AEs leading to discontinuation of investigational study treatment will be listed separately and, if appropriate, summarized by primary SOC and PT. To summarize, the following AE summaries will be presented for non-ocular, study eye, and fellow eye AEs (if applicable) for the TEAE safety observation period:

- all AEs
- AEs by maximum severity
- SAEs
- AEs leading to investigational study treatment discontinuation
- AEs suspected to be related to investigational study treatment
- AEs suspected to be related to ocular injection
- AEs suspected to be related to investigational study treatment and/ or ocular injection.

All information pertaining to AEs noted during the study (including AEs during the screening period, TEAEs and AEs during the post-treatment period) will be listed by patient, detailing AE (e.g., verbatim given by the investigator as well as the SOC and PT according to MedDRA), date of starting and ending, severity, suspected relationship (by the investigator) to the study drug/ ocular injection, and eye (for ocular events). The AE onset will also be shown relative (in number of days) to the day of (first) initial study treatment.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on TEAEs which are not serious adverse events with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the Safety Set.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is <= 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE/ SAE suspected to be related to study treatment/ non SAE has to be checked in a block e.g., among AE's in a <= 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

The following AE by-patient listings will also be provided:

- deaths
- SAEs
- AEs leading to investigational study treatment discontinuation
- AEs related to ocular/ systemic risks
  - Ocular/ systemic risks will be defined based on important identified and potential risks as outlined in the most recent version of the Risk Management Plan (RMP)
- all AEs
- AEs suspected to be related to investigational study treatment and/ or ocular injection.

2.9.2 Intraocular pressure

IOP absolute values and changes (pre-injection) from baseline by visit and changes from pre-dose to post-dose assessments within a visit will be descriptively summarized. Additionally, the number and percentage of patients with baseline IOP >= 25 mmHg will be presented by visit (pre-injection, post-injection assessment [if applicable]). Summaries will be presented separately for the study eye from baseline to EoT period.

All IOP data will be listed for all patients and baseline IOP values >= 25 mmHg will be flagged.

2.9.3 Vital signs

Vital signs (sitting systolic blood pressure, sitting diastolic blood pressure, sitting pulse, weight) will be summarized by descriptive statistics, by visit, presenting absolute and change from baseline values. Analysis will be based on the patients in the Safety Set for the baseline to EoT period. Using the critical values outlined in Table 2-4, a shift table will be produced to summarize the shift from baseline to any vital signs values that are abnormally low or high. All data, including data from unscheduled visits, will be considered when identifying abnormal values.

By-patient listings will be provided for all vital signs data and values outside the clinical normal ranges (see Table 2-4) will be flagged.

Table 2-4 Vital signs critical values

Variable	Type of abnormality	Criterion
Systolic blood pressure (mmHg)	High	Either ≥180 absolute with an increase from baseline ≥20 absolute
	Low	Either ≤90 absolute with an decrease from baseline ≥20 absolute
Diastolic blood pressure (mmHg)	High	Either ≥105 absolute with an increase from baseline ≥15 absolute

Variable	Type of abnormality	Criterion
	Low	Either ≤50 absolute with an decrease from baseline ≥15 absolute
Pulse rate (bpm)	High	Either ≥120 absolute with an increase from baseline ≥15 absolute
	Low	Either ≤50 absolute with an decrease from baseline ≥15 absolute

2.9.4 Laboratory evaluation

HbA1c and lipid levels will be presented using standard international (SI) units. Laboratory data - observed values or changes from baseline values at each visit - will be summarized using descriptive statistics. Analysis will be based on the patients in the Safety Set for the baseline to EoT period.

Two sets of shift tables will be provided. First, using the laboratory defined normal ranges from the raw data, a shift table will be produced to summarize the shift from baseline to any laboratory values that are abnormally low or high. All data, including data from unscheduled visits, will be considered when identifying abnormal values.

Second, clinical critical values are defined in Table 2-5. Baseline critical values are defined by the absolute values only. Using these critical values, a shift table will be produced to summarize the shift from baseline to any laboratory values that are abnormally low or high. All data, including data from unscheduled visits, will be considered when identifying abnormal values.

By-patient listings will be provided for all laboratory data. Values outside the clinical normal ranges will be flagged.

Table 2-5 Critical values for laboratory values

Variable	Type of abnormality	Critical values
Cholesterol	Out of normal range (low): female	2.38 mmol/l; 92 mg/dl
	Out of normal range (low): male	2.12 mmol/l; 82 mg/dl
	Out of normal range (high): female	6.06 mmol/l; 234 mg/dl
	Out of normal range (high): male	4.97 mmol/l; 192 mg/dl
	Pathologic value: female and male	6.22 mmol/l; 240 mg/dl
	Extremely pathologic value: female and male	9.07 mmol/l; 350 mg/dl
HDL-Cholesterol	Out of normal range (low)	1.04 mmol/l; 40 mg/dl
	Pathologic value (low)	0.91 mmol/l; 35 mg/dl
	Extremely pathologic value (low)	0.65 mmol/l; 25 mg/dl
LDL-Cholesterol	Out of normal range (high)	3.38 mmol/l;130 mg/dl

Variable	Type of abnormality	Critical values
	Pathologic value (high)	4.94 mmol/l; 190 mg/dl
	Extremely pathologic value (high)	6.50 mmol/l; 250 mg/dl
Triglycerides	Out of normal range (high)	1.71 mmol/l;150 mg/dl
	Pathologic value (high)	3.42 mmol/l; 300 mg/dl
	Extremely pathologic value (high)	5.13 mmol/l; 450 mg/dl
HbA1c	Out of normal range (high)	6.2%
	Pathologic value (high)	6.8%
	Extremely pathologic value (high)	14.6% (deviation alert above 12.1%)

2.10 Pharmacokinetic endpoints

Not applicable.

2.11 PD and PK/PD analyses

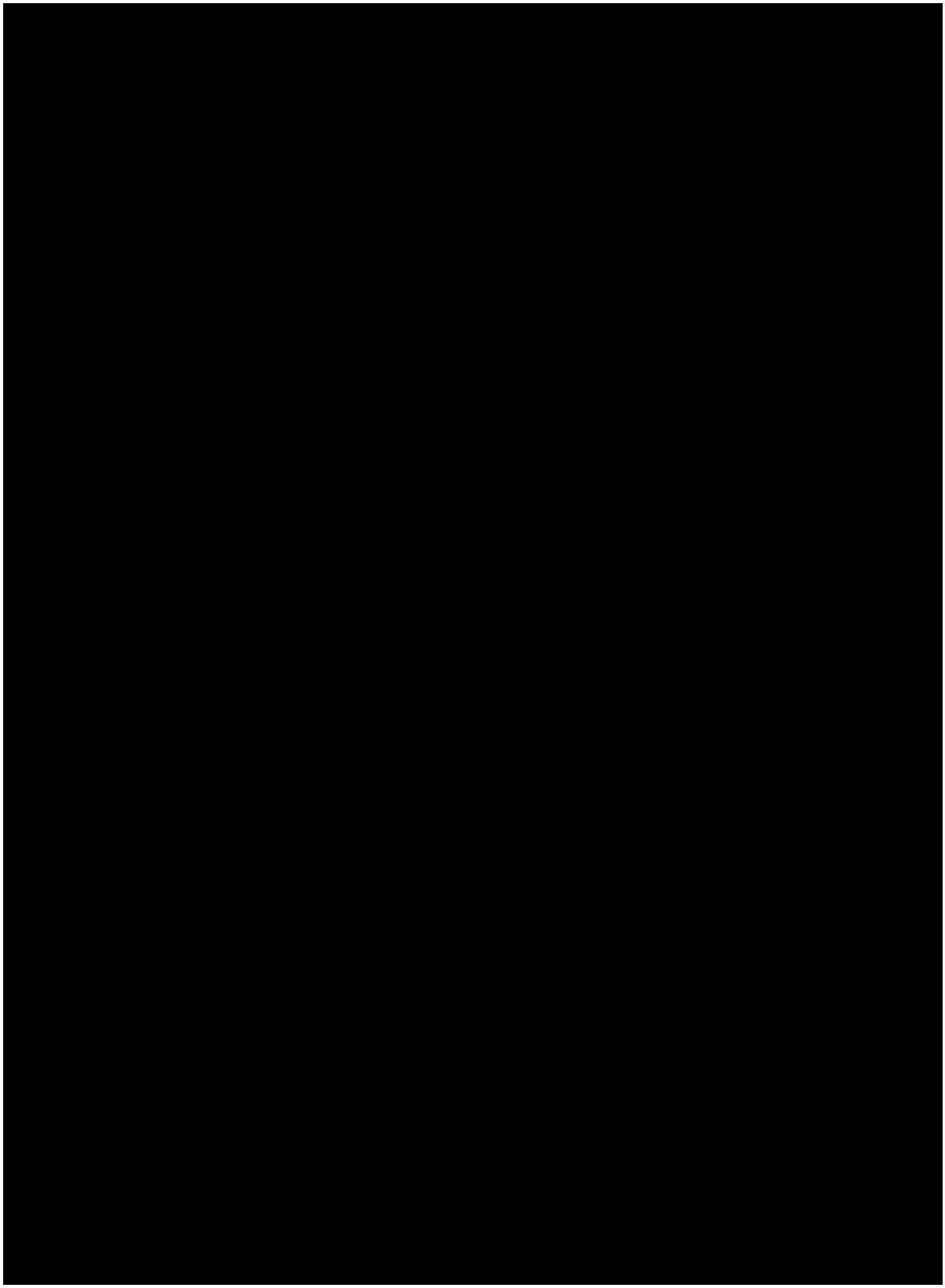
Not applicable.

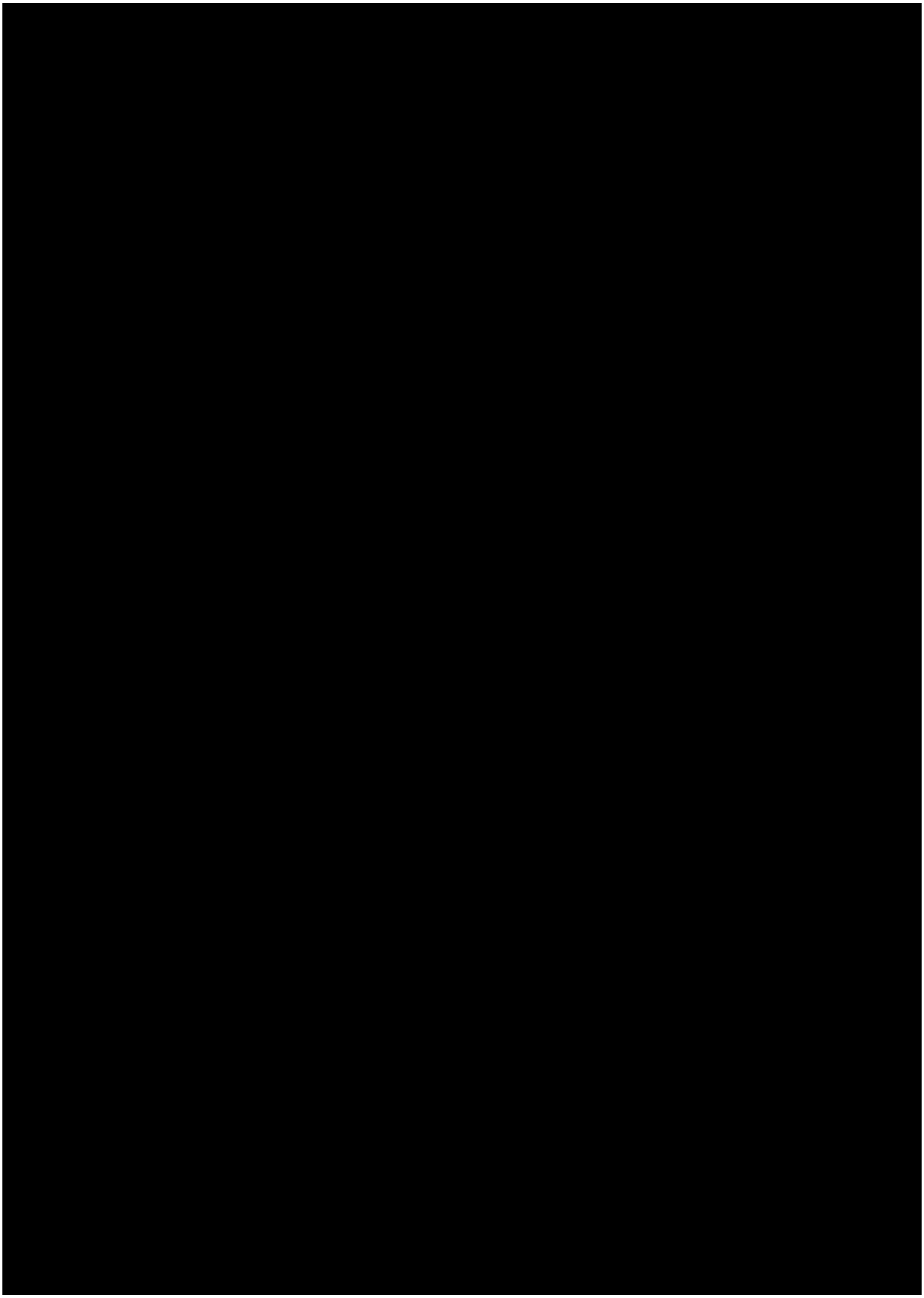
2.12 Patient-reported outcomes

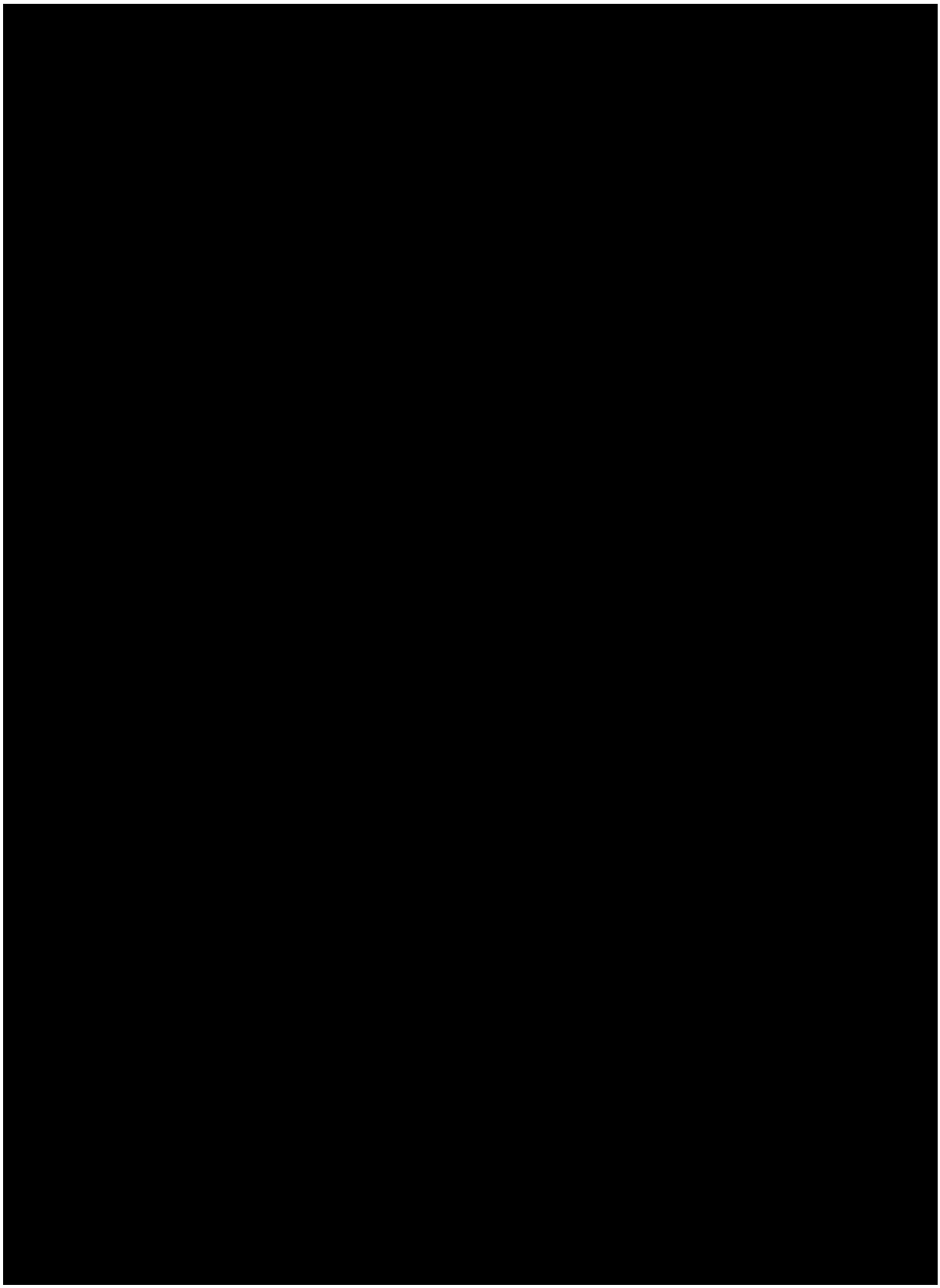
Not applicable.

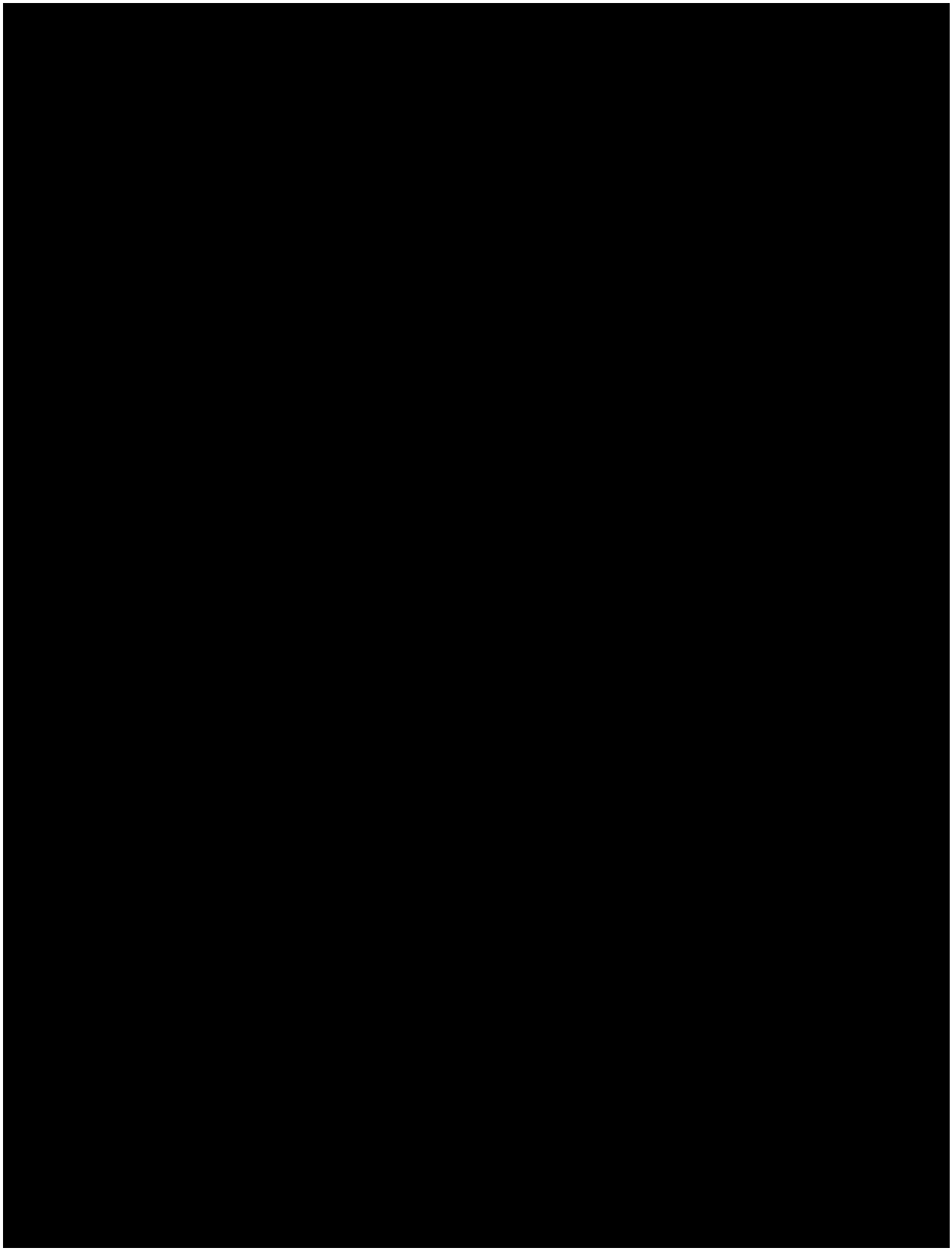
2.13 Biomarkers

Not applicable.









2.15 Interim analysis

No interim analyses will be performed.

3 Sample size calculation

A sample size of 133 patients per treatment arm will have 90% power to establish non-inferiority at a margin of 4 letters for the 0.5 mg ranibizumab "at investigators discretion" dosing regimens in comparison to 0.5 mg ranibizumab PRN in the mean average change in BCVA based on a one-sided 0.025 significance level, assuming a treatment difference of 0 letters, a SD of 10 letters and an underlying normal distribution for an unstratified t-Test (nQuery Advisor 7.0).

The Phase III study (RESTORE) results in the FAS suggest a mean average change in BCVA of 6 letters with a SD of about 7-8 letters for ranibizumab. To account for some more variability related to the re-treatment concepts and subgroup treated with additional PRP laser in this study as compared to RESTORE, a SD of 10 letters is assumed. To account for some drop outs 150 patients will be randomized per treatment arm.

As outlined in the study protocol, section "Summary of protocol amendments" (study protocol version no.1 including Amendment 1); further recruitment of patients into this study was revised and reduced. New and relevant scientific evidence regarding treatment patterns with ranibizumab was published which did not justify continuing the trial with newly included

patients. Therefore recruitment was terminated at the time when 135 patients were enrolled into the study, resulting in a reduced sample size present for analysis.

As a consequence results are to be interpreted in a purely descriptive manner. With an estimate of about 120-150 patients to be enrolled by end of recruitment the expected power would be about 55-60% and will be evaluated accordingly.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Adverse Events date imputation

5.1.1.1 AE start date imputation

The following table explains the notation used in the logic matrix. Please note that completely missing start dates will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

- If the (imputed) AE end date is complete and the (imputed) AE end date < investigational study treatment start date then AE start reference date = min(informed consent date, earliest visit date).
- Else AE start reference date = investigational study treatment start date

Impute AE start date:

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
   a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JULYYYY).
   b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the investigational study treatment start date year value, the AE started after treatment. Therefore:
   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JANYYYY).
   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the investigational study treatment start date year value:
   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
   b. Else if the AE month is less than the investigational study treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the investigational study treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.1.2 AE end date imputation

For the purpose of date imputation the treatment follow up period date is defined as the last available visit date, i.e. including unscheduled visits after the end of study visit.

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.
4. If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

5.1.2 Concomitant medication date imputation

5.1.2.1 CM start date imputation

The following table explains the notation used in the logic matrix. Please note that completely missing start dates will not be imputed.

	Day	Month	Year
Partial CM Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the investigational study treatment start date year value, the CM started before treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the mid –year point (01JULYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the investigational study treatment start date year value, the CM started after treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the year start point (01JANYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the investigational study treatment start date year value:
   a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior to treatment start date.
   b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
   c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

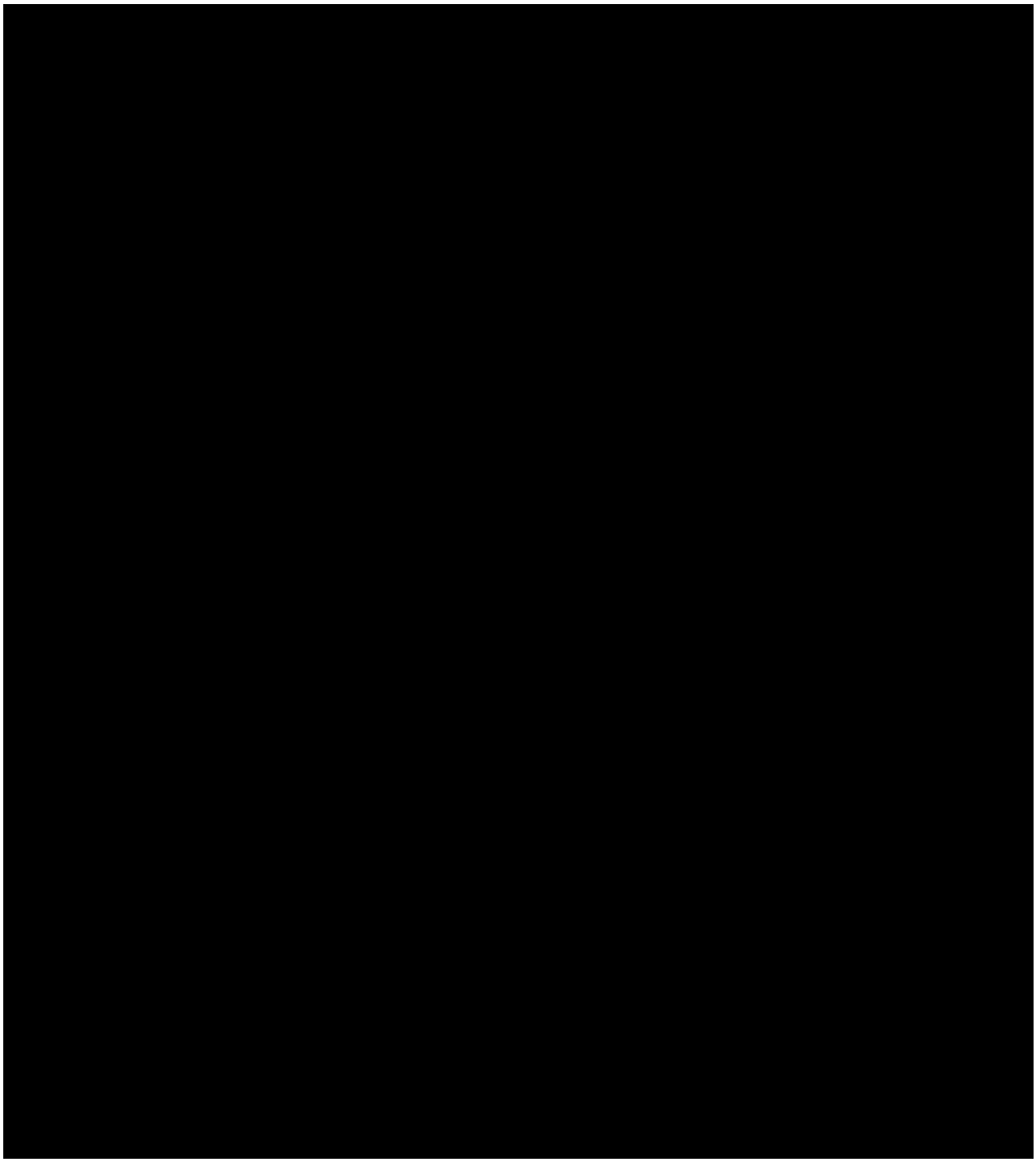
5.1.2.2 CM end date imputation

1. If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.
2. Else, if the CM end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
3. If the CM end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).
4. If the imputed CM end date is less than the existing CM start date, use the CM start date as the imputed CM end date.

5.1.3 Medical history date of diagnosis imputation

Completely missing dates and partially missing end dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

- If year of diagnosis (or DIAG year) < investigational study treatment start date year
  - and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY)
  - else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY)
- If DIAG year = investigational study treatment start date year
  - and (DIAG month is missing OR DIAG month is equal to investigational study treatment start month), the imputed DIAG date is set to one day before investigational study treatment start date
  - else if DIAG month < investigational study treatment start month, the imputed DIAG date is set to the midmonth point (15MON YYYY)
  - else if DIAG month > investigational study treatment start month → data error
- If DIAG year > investigational study treatment start date year → data error



5.2 Efficacy variables and populations for analysis

Table 5-3 describes and summarizes the efficacy variables of the study eye, and the populations for the planned analyses.

Table 5-3 Efficacy variables of the study eye

		Analysis		
Efficacy assessment	**Variable**	**Method**	**Population**	**Time Period**
Primary efficacy				
BCVA	Visit-averaged change from baseline in BCVA	ANCOVA[1]	FAS (LOCF)	Baseline – EoT
		ANCOVA[1]	PPS (LOCF)	Baseline – EoT
		ANCOVA[1]	FAS (as observed)	Baseline – EoT
		ANCOVA[1]	FAS (LOCF)	Baseline – EoS
		MMRM[1]	FAS (LOCF)	Baseline – EoT
	Secondary efficacy			
BCVA	BCVA change from baseline to month 12	ANCOVA[1]	FAS (LOCF)	Baseline - EoT
	BCVA change from baseline to month 12	ANCOVA[2]	FAS (LOCF)	Baseline - EoT
CSRT	CSRT change from baseline to month 12	ANCOVA[1]	FAS (LOCF)	Baseline - EoT
FCP thickness	FCP thickness change from baseline to month 12	ANCOVA[1]	FAS (LOCF)	Baseline - EoT

[1] The model includes the respective baseline variable as a linear covariate and the following categorical variables: treatment, center

[2] The model includes the respective baseline variable, relevant changes of HbA1c, blood pressure (systolic, diastolic), and lipid levels (cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) as linear covariates and the following categorical variables: treatment, center

5.2.1 SAS code for analysis

==========

SAS code for ANCOVA analysis

ANCOVA model will contain ‘treatment’ and ‘center’ as categorical variables, and ‘baseline BCVA’ as continuous. For secondary analysis additional linear covariates might be included, such as ‘HbA1c’, ‘Blood pressure (systolic, diastolic)’, or ‘Lipid levels (cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides)’.

For the appropriate treatment difference, the treatment arms should be sorted or coded appropriately before using this model.

The ANCOVA analysis will be performed using SAS procedure PROC MIXED as below. Note that for this illustrative example:

- the data are stored in the file data_set
- treatmentvar = treatment variable

- responsevar = dependent variable
- stratavar = stratification variable
- bsl = baseline value of the responsevar
- alpha = significance level (i.e. 0.05 produces two-sided 95% CI)
- control = control arm (Ranibizumab 0.5 mg in PRN treatment regime)

```
PROC MIXED DATA = <data_set>;
CLASS <stratavar> <treatmentvar>;
MODEL <responsevar> = <stratavar> <treatmentvar> <bsl>;
LSMEANS <treatmentvar> / PDIFF = all CL alpha = <alpha> OM;
RUN;
```

To get the one-sided p-value for the non-inferiority test (margin = 4): add -4 letters to control group and re-run the above code with alpha=0.025 and PDIFF=controlu('<control> ').

To get the one-sided p-value for the superiority test (if applicable): re-run the above code with alpha=0.025 and PDIFF=controlu('<control> ').

==========

SAS code for MMRM analysis

Since scheduled visit is in the repeated statement it is important to ensure that each patient has, at most, one observation per scheduled visit. This should be checked using PROC SORT and NODUPKEY.

To avoid potential problems with a bug in SAS reporting an infinite likelihood, the data will be sorted by patient and visit before using PROC MIXED.

For the appropriate treatment difference, the treatment arms should be sorted or coded appropriately before using this model.

The comparison of interest is found by using the SAS code below. Note that for this illustrative example:

- the data are stored in the file data_set
- treatmentvar = treatment variable
- subjvar = patient identifier
- responsevar = dependent variable
- stratavar = stratification variable
- visitvar = timepoint variable
- bsl = baseline value of the responsevar
- cov = covariance structure
- alpha = significance level (i.e. 0.05 produces two-sided 95% CI)
- control = control arm (<control>)

```
PROC SORT DATA = data_set OUT = s_data_set nodupkey;
BY patient visit;
RUN;
PROC MIXED DATA = <s_data_set> METHOD=REML;
CLASS <treatmentvar> <visitvar> <subjvar>;
MODEL <responsevar> = <stratavar> <treatmentvar> <visitvar>
<treatmentvar>*<visitvar> <bsl> <visitvar>*<bsl> / SOLUTION DDFM = KR;
REPEATED <visitvar> / SUBJECT = <subjvar> TYPE = <cov> r rcorr GROUP =
<treatmentvar>;
ESTIMATE 'Average Treatment Effect'
                  <treatmentvar> -1 1
                  <treatmentvar>*<visitvar> -0.083 -0.083 -0.083 -0.083 -0.083
                                            -0.083 -0.083 -0.083 -0.083 -0.083
                                            -0.083 -0.083
                                             0.083 0.083 0.083 0.083 0.083
0.083 0.083 0.083 0.083 0.083 0.083 0.083 /cl;
RUN;
```

Using the slice option above means that the difference between treatment arms will be tested for each visit.

To get the one-sided p-value for the non-inferiority test (margin = 4): add -4 letters to control group and re-run the above code with alpha=0.025 and PDIFF=controlu('<control> ').

To get the one-sided value for the superiority test (if applicable): re-run the above code with alpha=0.025 and PDIFF=controlu('<control> ').

If the model with the unstructured correlation matrix fails to converge then modifications shall be made in the following order.

1. Re-instate the GROUP = trtc option and replace un by VC
2. Re-instate the GROUP = trtc option and replace un by CS
3. Re-instate the GROUP = trtc option and replace un by AR(1)
4. Re-instate the GROUP = trtc option and replace un by TOEP
5. Remove the GROUP = trtc option and replace un by VC
6. Remove the GROUP = trtc option and replace un by CS
7. Remove the GROUP = trtc option and replace un by AR(1)
8. Remove the GROUP = trtc option and replace un by TOEP

Removing the GROUP = trtc option assumes that the correlation matrix is equal across the treatment arms. The other modifications replace the unstructured correlation matrix by those with the following assumptions (in the same order) variance components, compound symmetry, first order autoregressive and Toeplitz.

==========

SAS code for backward stepwise regression analysis

For the appropriate treatment difference, the treatment arms should be sorted or coded appropriately before using this model.

The analysis will be performed using SAS procedure PROC GLMSELECT as below. Note that for this illustrative example:

- the data are stored in the file data_set
- treatmentvar = treatment variable
- responsevar = dependent variable
- stratavar = stratification variable
- bsl = baseline value of the responsevar
- alpha = significance level (i.e. 0.05 produces two-sided 95% CI)
- n = the first ***n*** effects listed in the MODEL statement which are forced to be included in all models

```
PROC GLMSELECT DATA = <data_set>;
CLASS <stratavar> <treatmentvar>;
MODEL <responsevar> = <stratavar> <treatmentvar> <bsl> / DETAILS = all SELECTION =
backward INCLUDE = <n>;
LSMEANS <treatmentvar> / PDIFF = all CL alpha = <alpha> OM;
RUN;
```

==========

SAS code for Wilcoxon rank sum test

Wilcoxon Rank Sum Test will be presented as a nonparametric comparison additionally to the primary analyses.

For the appropriate treatment difference, the treatment arms should be sorted or coded appropriately before using this model.

Wilcoxon Rank Sum Test will be presented as a non-parametric comparison additionally to the primary analyses.

- the data are stored in the file data_set
- treatmentvar = treatment variable
- responsevar = dependent variable
- alpha = significance level

```
PROC NPAR1WAY DATA = <data_set> HL alpha = <alpha>;
CLASS <treatmentvar>;
VAR <responsevar>;
RUN;
```

==========

SAS Codes for Kaplan-Meier Plot

The time to event analysis will be performed using the SAS procedure PROC LIFETEST.

Note that for this illustrative example:

- the data are stored in the file data_set
- timevar = survival time
- censorvar = censoring variable (Note: 1 indicates a censored time)
- stratavar = stratification variable

```
ODS GRAPHICS ON;
PROC LIFETEST DATA=<data_set> PLOTS=survival (failure test at
risk(outside(0.15))=0 to 360 by 30);
TIME <timevar> * <censorvar> (1);
STRATA <stratavar>;
RUN;
```

The option OUTSIDE(0.15) reserves 15% of the vertical graph window for the at-risk table. It can be adjusted.

==========

SAS Codes for Kaplan-Meier Table

The summary statistics for time to event analysis will be performed using SAS procedure PROC LIFETEST.

Note that for this illustrative example:

- the data are stored in the file data_set
- timevar = survival time
- censorvar = censoring variable (Note: 1 indicates a censored time)
- stratavar = stratification variable

```
PROC LIFETEST DATA = <data_set>;
TIME <timevar> * <censorvar> (1);
STRATA <stratavar>;
 ODS OUTPUT CensoredSummary=censorsum
            Means=mean
            Quartiles=quartiles;
RUN;
```

==========

SAS Codes for Pearson's and Spearman's correlation coefficient

Pearson's and Spearman's correlation coefficient will be obtained using SAS procedure PROC CORR.

Note that for this illustrative example:

- the data are stored in the file data_set
- var1 = variable 1 to obtain the correlation of variable 1 and variable 2
- var2 = variable 2 to obtain the correlation of variable 1 and variable 2

```
PROC CORR DATA = <data_set> PEARSON SPEARMAN;
VAR <var1> <var2>;
RUN;
```

5.3 Rule of exclusion criteria of analysis sets

Table 5-4 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion from Analyses
I00	Not signed Informed Consent	Excluded from all analysis
I01	Subject is less than 18 years of age or age missing.	Not reportable
I02aa	Patients with diabetes but type of diabetes is not known.	Not reportable
I02ab	Patient with no History of diabetes.	Excluded from PP analysis
I02b	Glycosylated hemoglobin greater than 12 percent, i.e. 107 mmol per mol Hb, at screening Visit 1	Reportable
I03a	Patients without visual impairment due to DME in the study eye	Excluded from PP analysis
I03b	Patients without visual impairment due to DME in the fellow eye	Not reportable
I04a	BCVA less than 24 in the study eye, using ETDRS-like visual acuity testing charts at a testing distance of 4 resp. 1 meters (approximate Snellen equivalent of 20/32 to 20/320) at screening or baseline	Not reportable
I04b	BCVA greater than 78 in the study eye, using ETDRS-like visual acuity testing charts at a testing distance of 4 resp. 1 meters (approximate Snellen equivalent of 20/32 to 20/320) at screening or baseline	Excluded from PP analysis
I05	Concomitant conditions in the study eye, which prevent improvement of visual acuity on study treatment	Excluded from PP analysis (medical review)
E01aa	Active intraocular inflammation grade trace or above in the study eye at enrollment.	Excluded from PP analysis (medical review)
E01ab	Active intraocular inflammation grade trace or above in the fellow eye at enrollment.	Not reportable
E01a	Women who are pregnant or breast feeding.	Not reportable
E02	Any active infection in either eye at the time of enrollment e.g. conjunctivitis, keratitis, scleritis, endophthalmitis.	Reportable (medical review)
E03	History of uveitis in either eye at any time.	Not reportable
E04	Structural damage within 0.5 disc diameter of the center of the macula in the study eye likely to preclude improvement in VA, incl. atrophy of RPE, subretinal fibrosis, laser scar(s).	Excluded from PP analysis (medical review)
E05	Patients with both, a BCVA score of greater than 73 letters and a central subfield thickness of less than 300 micro meter in the study eye.	Excluded from PP analysis (medical review)
E06	Uncontrolled glaucoma in either eye at screening. IOP greater than 24 mmHg on medication or according to investigator judgment.	Excluded from PP analysis (medical review)
E07	Neovascularization of the iris in either eye.	Not reportable
E08	Vitreous hemorrhage impairing the adequate diagnosis of DME in the	Excluded from

Deviation ID	Description of Deviation	Exclusion from Analyses
	study eye.	PP analysis
E09	Clinically relevant vitreofoveal adhesion, vitreofoveal traction or epiretinal membrane with foveal involvement likely to prevent improvement of BCVA, according to investigator opinion.	Not reportable
E10	Proliferative vitreoretinopathy in study eye.	Not reportable
E11	History of retinal detachment, retinal tear or macular hole in the study eye.	Not reportable
E12	Neovascularization covering an area greater than or equal to 2 disc areas within the macula defined as area with 6mm diameter centered on the fovea for study eye.	Not reportable
E13	Patients who are monocular or have a BCVA score in the non-study eye less than 24 letters approximate Snellen equivalent of 20 per 320 at Visit 1.	Not reportable
E14	Any intraocular surgery in the study eye within 4 months prior to randomization.	Reportable (medical review)
E15a	Vitrectomy/vitreoretinal surgery - In the medical history or planned for study eye.	Reportable (medical review)
E15b	Planned vitrectomy or vitrectomy in last 3 months in fellow eye.	Not reportable
E16	Planned medical or surgical intervention during the 12 months study period likely to interfere with study schedule or outcomes.	Reportable (medical review)
E17	Panretinal or focal or grid laser photocoagulation in study eye within 3 months prior to randomization unless sufficient documentation of laser photocoagulation in that period of time is available.	Reportable (medical review)
E18a	Treatment with anti-angiogenic drugs within 1 month for fellow eye prior randomization.	Not reportable
E18b*	Treatment with anti-angiogenic drugs within 3 months (84 days) for study eye prior randomization.	Excluded from PP analysis
E19	Use of other investigational drugs at the time of enrollment, or within 3 months or 5 half-lives from enrollment, whichever is longer.	Reportable (medical review)
E20	History of intravitreal corticosteroid treatment in phakic study eye.	Reportable (medical review)
E21	Intravitreal corticosteroids in post-cataract surgery study eye (aphakic or pseudophakic, without damaged posterior capsule) within 3 months or 6 months for dexamethasone implant (Ozurdex®) or 3 years for fluocinolone implant (Iluvien®) prior to randomization.	Excluded from PP analysis
E22	Ocular conditions in the study eye that require chronic concomitant therapy with topical ocular corticosteroids.	Reportable (medical review)
E23	Stroke less than 4 months prior to screening.	Not reportable
E24	Renal failure requiring dialysis or renal transplant.	Not reportable
E25	Untreated diabetes mellitus.	Not reportable
E26	BP defined as systolic value of greater than 160 mm Hg or diastolic value greater than 100 mm Hg at screening or randomization.	Not reportable
E27	Conditions that require chronic concomitant therapy with systemically administered corticosteroids.	Reportable (medical review)
E28	Current use of Medications known to be toxic to the lens, retina or	Reportable

Deviation ID	Description of Deviation	Exclusion from Analyses
	optic nerve, including Deferoxamine, Chloroquine or hydroxychloroquine, Plaquenil, Tamoxifen, Phenothiazines and Ethambutol.	(medical review)
E29	Use of any systemic anti VEGF drugs within 3 months prior to Screening.e.g. bevacizumab, ziv aflibercept.	Excluded from PP analysis
E30	Known hypersensitivity to fluorescein or ranibizumab or any component thereof or drugs of similar chemical classes.	Not reportable
E31	Disease severity/medical condition/ treatment expected to progress, recur, or change to an extent may bias the assessment of clinical status of patient or special risk to a significant degree.	Reportable (medical review)
D01	MH or AE - Rhegmatogenous retinal detachment or Stage 3 or 4 macular hole in the study eye and no treatment discontinuation.	Excluded from PP analysis (medical review)
D02	MH or AE - Transient ischemic attack or a stroke during the study and no treatment discontinuation	Not reportable
D03	Pregnancy but patient not discontinued from trial.	Excluded from PP analysis
D04	Vitrectomy that did not lead to discontinuation of study treatment.	Excluded from PP analysis
S01	Patient received Ranibizumab from another study or as commercially available Lucentis	Not reportable
S02	Study task injection of ranibizumab was performed by untrained site personnel.	Not reportable
S03	Patient received study medication which was outside the allowed temperature range and should have not been used any more according to guidelines or QP decision.	Reportable (medical review)
M01	Concurrent use of any anti-VEGF agents either systemic or in the study eye (only permitted in the fellow eye).	Excluded from PP analysis
M02	Concurrent use of peribulbar or intraocular corticosteroids in study eye.	Excluded from PP analysis
M03	Concurrent use of intraocular corticosteroids inserts in study eye.	Excluded from PP analysis
M04	Systemic medications known to be toxic to the lens, retina or optic nerve, including Deferoxamine, Chloroquine or hydroxychloroquine, Tamoxifen, Phenothiazines and Ethambutol.	Reportable (medical review)
M05	Treatment with glitazones or fingolimod when newly started during the study.	Reportable (medical review)
M06	Other investigational drugs and interventions of any type.	Excluded from PP analysis
[redacted]	[redacted]	[redacted]
O02	Missing FLA assessment at visit 1 for both eyes.	Not reportable
O03	Missing FLA assessment at visit 14 for both eyes.	Not reportable
O04a	Missing FP assessment at visit 1 for both eyes.	Not reportable
O04b	Missing FP assessment at EOS visit for both eyes.	Not reportable

Deviation ID	Description of Deviation	Exclusion from Analyses
O05	Missing BCVA in study eye at any visit.	Not reportable
O06	Missing BCVA in fellow eye at any Screening, EOS and EOT visits.	Not reportable
O07	Missing OCT assessment in study eye at any visit.	Not reportable
O08	Missing OCT assessment in fellow eye at Screening, EOS and EOT visits.	Not reportable
O09a	Intraocular Pressure was not measured prior treatment for study eye.	Not reportable
O09b	Intraocular Pressure was not measured after treatment for study eye.	Not reportable
O10	Inadequate training of Investigators during study conduct.	Not reportable
O12	Screening not 28 to 3 days before Baseline.	Not reportable
O14	End of Study Visit not after last treatment of study medication.	Not reportable
O15	Focal or grid laser photocoagulation done prior 3 months after baseline.	Reportable (medical review)
O16	Any Treatment cycle (PRP) was not completed within 6 weeks	Reportable (medical review)
O17	Panretinal Photocoagulation at baseline or at least within 3 months after randomization in both arms for study eye for respective patients	Reportable (medical review)
O19	PDR laser spots smaller than 500 micro meter for respective patients	Not reportable
O20	Less than 12 weeks between PRP-treatments for respective patients	Not reportable
O21	VA examination done by non-certified personnel for both eyes or study eye only.	Not reportable
O22	OCT examination done by personnel not certified for study.	Not reportable
O23	OCT examination done with a device not registered for study.	Not reportable
[redacted]	[redacted]	[redacted]
O25	FP examination done with a device not registered for study.	Not reportable
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
O28	BCVA examination done in a non-certified room.	Not reportable
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
O31	General GCP or CSP compliance issue.	Not reportable
O32	VA assessor did not change from Visit 1 to Visit 4 (same at any 2 consecutive visits up to V4).	Not reportable
O33	VA assessor did not change from Visit 5 onwards (same at any 2 consecutive visits from V5 onwards).	Reportable
O35**	BCVA measurement was performed 2 days later then visit 1. V1 was split in 2 days.	Not reportable
O37	Same BCVA-Assessor at consecutive months visit 5 onwards.	Reportable
O39	BCVA assessor, who performed other study tasks and was subsequently unmasked to treatment arm, was still active as BCVA assessor.	Reportable

Deviation ID	Description of Deviation	Exclusion from Analyses
O40	Minimum PRP treatment of 1200 burns for study eye was not given for respective patients.	Reportable (medical review)
O41	Subjects who had completed trial and have number of days difference between V2 to V14 (EOS) is above 393 days.	Excluded from PP analysis
O42	Minimal Injection window period must be 28 days.	Not reportable

* In PD E18b the 3 months criterion was clarified to be 84 days (which is based on 7 days by 4 weeks by 3 months)

** PD O34 was retired as a PD and will only be handled as an edit check by data management in the database

6 Reference

(1) CRFB002DDE26 Protocol

- CREDI Projects/R/RFB002D/CREDI Studies/RFB002DDE26/CSP (Clinical Study Protocol) – CRFB002DDE26_CSP_V01

(2) CRFB002 Project Master Analysis Plan (MAP) Version 2.0

- CREDI Projects/R/RFB002A/Administrative files/CIS (Clinical Information Sciences)/Biostatistics – CRF002 MAP Module 3 Detailed statistical methodology_v2

(3) Han IC, Jaffe GJ (2009) Comparison of Spectral- and Time-Domain Optical Coherence Tomography for Retinal Thickness Measurements in Healthy and Diseased Eyes. American Journal of Ophthalmology 147:847-858.(4) Lang, GE et al. (2013) Two-Year Safety and Efficacy of Ranibizumab 0.5 mg in Diabetic Macular Edema: Interim Analysis of the RESTORE Extension Study. Ophthalmology 120(10): 2004-12

(5) Mitchell P et al. (2011) The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 118.4: 615-25

(6) Mylonas et al. (2009) Comparison of retinal thickness measurements and segmentation performance of four different spectral and time domain OCT devices in neovascular agerelated macular degeneration. British Journal of Ophthalmology 93:1453–1460.

(7) Schmidt-Erfurth U, Lang GE, Holz FG, Schlingemann RO, Lanzetta P, Massin P, Gerstner O, Bouazza AS, Shen H, Osborne A, Mitchell P: Three-Year Outcomes of Individualized Ranibizumab Treatment in Patients with Diabetic Macular Edema: The RESTORE Extension Study. Ophthalmology 2014.